REMARKS

Claims 1-15 are pending in this application. Claims 1-15 have been rejected. New claims 16 and 17 have been added to further define the invention. Support for new claim 16 is found in the specification at page 13, line 5. Support for claim 17 is found in the specification at page 16, lines 20-26 to page 17, lines 1, and 13-15. No new matter has been added.

Further and favorable reconsideration is respectfully requested in view of the following remarks.

I. At page 2 of the Office Action, claims 1-15 are rejected under 35 USC § 103(a) as being unpatentable over Akiyama et al. '006 in view of Sekigawa et al. '720, or vice versa.

The Examiner states that it would have been obvious to one of ordinary skill in the art to combine the teachings of Akiyama and Sekigawa, using the coating of Akiyama as the first layer, followed by the cellulose ether layer of Sekigawa, with an expected result of a coated medicament where the coating includes chitosan, a water-insoluble polymer and an enteric polymer. In view of the following this rejection is respectfully traversed.

Akiyama is directed to a gastrointestinal mucosa-adherent matrix including an active ingredient-containing core coated by a gastrointestinal mucosa-adherent coating composition which allows the matrix produced to attach to the gastrointestinal mucosa and remain within the gastrointestinal tract for a longer period of time, thus promoting absorption of the active ingredient which results in improved bio-availability, and achieves sustained release of the medicament.

The Akiyama matrix is solid at ambient temperature and includes matrix particles containing a polyglycerin fatty acid ester and/or a lipid, a medicament, and a viscogenic agent which becomes viscous on contact with water and is dispersed at least in the neighborhood of the surface layer of the matrix particles. (see Akiyama at column 2, lines 35-40). The viscogenic agent is defined in Akiyama, as anything that becomes viscous upon contact with water, and is adherent to the

gastrointestinal mucosa. Such substances include acrylic polymers/copolymers, cellulose ethers, polyethylene glycols, and naturally-occurring viscous substances including, for example, chitosan.

The object of Akiyama is to achieve adherence of the matrix to the gastrointestinal mucosa, thereby prolonging retention time of the matrix in the gastrintestinal tract.

Akiyama teaches that sustained release is affected by either forming a matrix with a polyglycerin fatty acid ester and/or a lipid, where the matrix per se is effective for releasing the medicament gradually, or by coating a bio-adherent component onto the matrix causing the active ingredient to release over a longer period of time. More specifically, the bio-adherent coating allows the matrix to adhere to the mucosa and thereby the preparation can be maintained within the biobody for a period of time longer than preparations not having such a coating. Thus, allowing the medicament to be continuously released for a longer period of time.

Sekigawa is directed to a coated solid medicament form suitable for oral administration having reliable release of the active ingredient in the large intestine only. Upon oral administration of the preparation, the preparation passes through the stomach and small intestine, and upon reaching the large intestine, the chitosan is decomposed by E. coli, and the medicament contained in the core is released at an accelerated rate.

The coated solid preparation of Sekigawa includes a core solid medicament form containing the active ingredient, a coating including chitosan having a specific degree of deacetylation and a specific degree of polymerization, and a specific enteric-soluble polymer top coating. Further, the core medicament form is provided with an enteric undercoating layer prior to coating with chitosan in order to achieve reliable release of the active ingredient in the large intestine only.

The enteric polymer top coating of Sekigawa includes a hydroxypropyl methyl cellulose hexahydrophthalate (see col. 5, lines 2-4, and the Abstract). The enteric undercoating layer, prior to coating with chitosan, includes hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, hydroxypropyl methyl cellulose hexahydrophthalate, cellulose acetate

phthalate, carboxymethyl ethyl cellulose, methacrylic acid copolymers, in the form of a solid or emulsion (see col. 5, lines 32-43).

The preparation of Sekigawa, having a more reliable releasability of the active ingredient, is a triple-coated solid medicament form which is composed of a medicament-containing core material having (i) an enteric undercoating layer, (ii) a chitosan coating layer, and (iii) an enteric top coating layer. Upon oral administration of this preparation, the preparation passes through the stomach and the small intestine unchanged. Once the preparation reaches the large intestine, the chitosan is decomposed by *E. coli* and the medicament contained in the core is released. When the preparation lacks an enteric undercoating layer, upon dissolution of the enteric top coating layer in the small intestine, the chitosan coating layer swells and the medicament is released through the swollen chitosan layer, to some degree. By providing the enteric undercoating layer, releasability in the large intestine only, is achieved.

The preparation of Sekigawa, includes chitosan that has a specific degree of deacetylation, and a specific degree of polymerization, and is applied to the core after dissolving in an acidic solution. Accordingly, the medicament contained in the core may be adversely affected by the acid remaining in the acidic solution of chitosan. In the present case, the chitosan powder can be any conventional chitosan powder, and is dispersed in the water-insoluble polymer without the use of an acidic solution.

The present invention is directed to a colonic delivery solid preparation, which passes through the gastrointestinal tract in a natural manner, including a medicament-containing solid material (core), a coating layer of a water-insoluble polymer where a chitosan powder is dispersed in the polymer and is provided on the core, and a coating layer including an enteric polymer provided on the polymer-chitosan layer. (please see claims 1-5, 10-15, and process claim 6). The present invention is also directed to a solid preparation, which passes through the gastrointestinal tract in a natural manner, including a medicament-containing solid material (core), and a coating layer or a water-insoluble

polymer where a chitosan powder is dispersed therein. (please see product claims 7-8 and process claim 9).

With regard to the first embodiment (claims 1-5, 10-15, and 16) including an enteric polymer coating layer, this preparation when orally administered passes through the stomach without change due to the outer enteric coating layer, and into the small intestinal tract, where the enteric coating is dissolved and removed. During passage through the small intestine, the medicament contained in the core is gradually released through the water-insoluble polymer in the inner coating layer. Once the preparation reaches the large intestine (colon), the chitosan powder dispersed within the water-insoluble polymer of the inner coating layer is decomposed by E. coli, resulting in the formation of a plurality of pores in the inner coating layer. As a result, the medicament contained in the core is further released through the pores.

The first embodiment including an enteric coating layer is useful for releasing medicament in the large intestine. By varying the specific water-insoluble polymer, the amount of polymer, the thickness of the coating, the type of chitosan powder, and the amount of chitosan powder, the region of release of the medicament in the gastrointestinal tract, and the speed or rate of release, can be controlled.

Regarding, the second embodiment (claims 7-8, and 17) not containing an enteric coating, upon oral administration of this preparation, the chitosan within the water-insoluble polymer coating layer is partially dissolved by acid in the stomach resulting in some pore formation in the coating layer through which the medicament contained in the core is partially released. During passage through the small intestine, the medicament is continuously released without further dissolution of the chitosan. After the solid preparation reaches the large intestine, the chitosan powder is decomposed by E. coli, thereby causing the medicament to be released at an accelerated rate.

The present preparation, including an enteric coating is useful for targeting release of a medicament in the large intestine. In both embodiments, the specific water-insoluble polymer, the amount of such polymer, the amount of chitosan powder, and the thickness of the chitosan powder-

dispersed water-insoluble polymer layer, can be varied to achieve release in a desired region of the intestine, and to achieve a desired rate of release.

It is submitted that a *prima facie* case of obviousness has not been established. A proper case of *prima facie* obviousness under 35 U.S.C.§103, requires that the prior art as a whole, must suggest the desirability of making the claimed combination and provide a reasonable expectation of success. In other words, reasons must be shown as to why the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed. There must be a teaching or suggestion within the prior art to select particular elements, and to combine them in the way they were combined by the inventor.

It is submitted that the combination of Akiyama with Sekigawa, is improper, because there is no teaching, suggestion, or motivation in either Akiyama or Sekigawa to support the combination.

The present composition is an encapsulated sustained-release preparation where a core containing a medicament is covered with a coating. The Akiyama preparation is a matrix-type preparation where the medicament is dispersed in a controlled release matrix. Accordingly, the present [illegible] different from the preparation of Akiyama.

[illegible] from any composition, that does not achieve sustained release and intestinal tract is not prolonged, because Akiyama ***requires*** both through the property of adherence, and sustained-release achieved release matrix composition. Specifically, prolonged retention of the stinal tract, is achieved by adhering the medicament-contained matrix

Thus, the skilled artisan in view of Akiyama, would have no motivation to look to Sekigawa, because Sekigawa teaches an encapsulated composition where the release of medicament occurs only in the large intestine, where such release is at a rapid rate, and the retention of the composition in the large intestine is not prolonged.

Sekigawa teaches a composition where the medicament is released ***only*** in large intestine, and not in the stomach and small intestine. Please see Sekigawa at col.1, lines 5-14. Sekigawa is not concerned with prolonging the retention of the composition in the large intestine.

Thus, the skilled artisan in view of Sekigawa, would have no motivation to look to Akiyama, because Akiyama teaches that the medicament of the matrix composition is preferably released at a constant rate in ***both*** the stomach and intestine irrespective of environmental pH. Please see Akiyama at col. 8, lines 39-41.

Assuming arguendo, the combination of Akiyama and Sekigawa is proper, it is submitted that a *prima facie* case of obviousness has still not been established.

There is no teaching or suggestion in either Akiyama or Sekigawa to select the first coating layer of Akiyama and combine it with the enteric coating layer of Sekigawa, to coat a solid medicament. Akiyama is directed to a matrix composition that adheres to the gastrointestinal mucosa, thereby achieving prolonged release in the large intestine. Akiyama ***requires*** that the matrix composition adhere to the mucosa. When the matrix composition of Akiyama is coated, Akiyama ***requires*** that the coating adhere to the gastrointestinal mucosa. Please see Akiyama at col. 1, lines 17-18, col. 2, lines 2-26, and col. 13, lines 14-16.

One of skill in the art, confronted with the present problem of achieving controlled release of a medicament in an encapsulated form, would have no motivation to look to Akiyama, to select the first coating of Akiyama, because Akiyama is directed to matrix compositions, not encapsulated compositions. Akiyama achieves controlled-release through the use of a medicament in combination with a controlled-release matrix, not through coating compositions, as does the present invention.

Further, one of skill in the art, would have no motivation to select the enteric coating layer of Sekigawa, because Sekigawa is concerned only with achieving release in the large intestine and not in the stomach or small intestine. Sekigawa teaches that release is rapid, and not controlled, once the composition reaches the large intestine.

Akiyama does not teach or suggest the present coating layer including a water-insoluble polymer having a chitosan powder dispersed therein, where the coating does not adhere to the gastrointestinal mucosa. The present composition does not adhere to the gastrointestinal mucosa, rather it passes in a natural manner through the digestive tract. Please see the specification at pages 13-17.

Sekigawa does not cure the deficiencies of Akiyama, since Sekigawa also does not teach or suggest the present coating layer including a water-insoluble polymer having a chitosan powder dispersed therein.

Accordingly, even if motivation to select the first layer of Akiyama and the enteric coating of Sekigawa existed, the present invention would not be achieved, because Akiyama requires that the coating adhere to the gastrointestinal mucosa to achieve prolonged presence in the large intestine, whereas the present preparation passes in a natural manner through the gastrointestinal tract.

Specifically, the present preparation naturally passes through the gastrointestinal tract, without prolonged retention in the gastrointestinal tract, as opposed to Akiyama. Please see the specification at pages 13-17. If the present preparation were adhered to the mucosa, the desired controlled release of medicament, could not be achieved.

Akiyama discloses numerous examples of viscogenic agents useful for achieving adherence to the gastrointestinal mucosa (please see Akiyama at col. 3, line 37 to col. 4, line 8). Chitosan is listed as one example among naturally-occurring mucous substances. However, the use of chitosan is not exemplified in Akiyama. In the present case, the chitosan powder is dispersed in a water-insoluble polymer coating layer and even if the chitosan in contact with water becomes viscous, the chitosan is dispersed in the polymer coating layer and cannot adhere to the gastrointestinal mucosa, as required by Akiyama.

Regarding Sekigawa, the chitosan-coating layer is rapidly decomposed in the large intestine to denude the medicament-containing core and thereby the medicament is released very rapidly. This very rapid release is problematic in that the medicament may be undesirably excessively released.

With regard to the present invention, the chitosan powder is dispersed in the water-insoluble polymer layer, and thus, even when the chitosan is decomposed in the large intestine, the medicament will be gradually released through the pores in the water-insoluble polymer layer formed by decomposing of the dispersed chitosan powder.

The present invention is also advantageous in that the medicament releasing point can be controlled by regulating the thickness of the chitosan powder-dispersed water-insoluble polymer layer. Further, since the medicament may also be released through the water-insoluble polymer layer to some extent, even though there is no lag until decomposition of the chitosan powder in the large intestine, no lag time exists in the initiation of release of medicament. However, in the preparation of Sekigawa, there is a time lag until release of medicament, because once reaching the large intestine, the chitosan must be decomposed prior to release of medicament. Thus, the present preparation achieves significantly improved sustained-release properties, as compared to Sekigawa. Further, Sekigawa preferably includes an enteric undercoating to achieve release in the large intestine only. The present preparation does not include an enteric undercoating.

Further, new claims 16-17 clearly define over Akiyama and Sekigawa. The preparation of Akiyama releases medicament in the stomach, contrary to the requirement of claim 16. The preparation of Akiyama does not provide an accelerated release in the large intestine, contrary to the requirement of claim 17. Moreover, the preparation of Akiyama does not pass through the stomach and small intestine but adheres to the mucosa therein.

In view of the above, it is submitted that nothing in Akiyama et al. and Sekigawa et al., taken alone or together, render the claimed invention obvious within the meaning of 35 USC § 103(a). Accordingly, the Examiner is respectfully requested to withdraw this rejection.

In view of the foregoing remarks, it is respectfully submitted that the application is in condition for allowance. Such allowance is solicited. If the Examiner has any questions regarding this response, the application in general, or has any suggestions for placing the application in condition for allowance, the Examiner is requested to call the undersigned at the number listed below.

Respectfully submitted,

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